(a) a first set of multiple features each of which has first polynucleotide molecules of at least 400 nucleotides in length; and

(b) a second set of features each of which has second polynucleotide molecules of no more than 100 nucleotides in length, each of which features contain a polynucleotide of only one sequence.

Remarks

The Examiner is thanked for the Office Action mailed 08/21/2002 (request for 1-month extension of time to respond, enclosed). In the Office Action Summary sheet, claims 1-37 are indicated as pending in the present application, and claims 1-21 and 23-36 are indicated as rejected. In view of the restriction requirement and the remainder of the Action, it is believed that only claims 1-21 have been examined and rejected, and thus only claims 1-20 and 38-41 are pending and under consideration in the present application. Confirmation of this is requested before cancellation of non-elected claims.

All of the pending claims (other than claim 41 discussed at the end of the "Remarks" section below) require that the first and second polynucleotides be single stranded. This is recited, for example on page 11, lines 1-2. New claim 41 recites that there is present a second set of features each of which has second polynucleotide molecules of no more than 100 nucleotides in length, each of which features contain a polynucleotide of only one sequence. Such a feature is recited, for example, on page 10, lines 28-29 of the present application.

The rejections contained in the Action are discussed in sequence below. Paragraph numbers in the sub-titles refer to paragraph numbers in the Action.

Paragraph 3

In paragraph 3 of the Action the Examiner first raised a number of 35 U.S.C. 112, second paragraph rejections which will be discussed in sequence below, with "a", "b" and the like referring to the lettered sub-paragraphs under paragraph 3 of the

Action. For brevity only the clarifying amendments to the claim language are discussed and the specific rejection is not repeated. The claims are not changed in scope by the present amendments but their existing scope merely even more clear.

a. Claims 2 and 3 have been amended to reference "a ratio".

b. Claims 2 and 3 have been amended to insert "of" in accordance with the Examiner's helpful suggestion.

c. Claim 8 has been amended with regard to antecedent basis for "stilt portion" by referring to "a stilt portion" and by adding the reference "if present" (since it may not be).

d. Claim 10 has been amended to insert "of" in accordance with the Examiner's helpful suggestion.

e. Clam 10 has been amended to make it clearer that the referenced some lines include features of both the first and second sets.

f. Claims 11 and 12 have been amended to refer to sequences of molecules recited in claim 1.

g. Claim 12 has been amended to replace "majority" with "more than half" (the dictionary 3a. from the Merriam-Webster on-line dictionary at www.merriam.com). The objected to language regarding 70% has now been further clarified.

h. Claim 13 has been amended similar to claims 11 and 12, to now refer to sequences of molecules in claim 1.

i. Claim 15 has been amended to remove "respective" and replace with equivalent, but clearer language.

j. Claim 16 has been amended to remove "respective" in a similar manner as claim 15.

k. The word "targets" has been removed from claim 17 to make it clear that the controls are labeled.

l. Claims 18 and 19 have been amended to change "the ratio" to "a ratio".

m. Claims 18 and 19 have been amended to insert "of" in accordance with the Examiner's helpful suggestion.

Paragraph 5

The Examiner rejected claims 1, 4-9, and 11-14 under 35 U.S.C. 102(b) as being anticipated by Adams et al. (US 6,060,288). In this rejection the Examiner stated that Adams et al. has first polynucleotides which are double stranded (those that were hybridized) and second polynucleotides which are single stranded (non-extended primers).

Other than claim 41, claims 1 and 15 are the only independent claims in the claims currently pending and under consideration. Both of those claims have been amended to recite that both the first and second polynucleotides are single stranded. Thus, both of these claims now refer to single stranded first polynucleotide molecules of at least 400 nucleotides in length, and single stranded second polynucleotide molecules of no more than 100 nucleotides in length. All of the non-extended primers in Adams et al. are less than 100 nucleotides in length (see, for example, column 2, lines 20-29) and Adams et al. does not disclose, nor provide any motivation for having, features with single stranded polynucleotides of at least 400 nucleotides and features with single stranded polynucleotides less than 100 nucleotides in length.

Accordingly, it is believed that the present rejection should now be withdrawn.

Paragraph 6

The Examiner next rejected claims 1 and 6-9 under 35 U.S.C. 102(e) as being anticipated by Chenchik et al. (US 6,087,102) as defined by Stewart, R. (A Few Words about DNA and Chromatin, dissertation, 1997, page 2). The Examiner refers to Column 8, lines 15-21 of Chenchik et al. for disclosing features of different length which are collected from fractions ranging from 10^3 daltons (10 nucleotides) to 10^6 daltons (10,000 nucleotides) which are arranged according to size (referring to Claims 8-12 of Chenchik et al). However, the referenced Column 8, lines 13-21 of Chenchik et al. read as follows:

> "For discontinuous size separated patterns, the initial complex mixture of target molecules will be separated into a plurality of fractions, wherein each fraction consists of a range of molecular weights, i.e. the member compounds of each fraction will fall within a range of molecular weights, **where the magnitude of the range in**

> **each fraction will be** at least 10^3 daltons and usually at least $2 \cdot 10^3$ daltons and may be as large as $5 \cdot 10^3$ daltons or larger, but will usually not exceed about 10^6 daltons and more usually will not exceed about 10^5 daltons."

Thus, the above portion of Chenchik et al. which the Examiner references does not in fact disclose both a first set of features each of which has single stranded first polynucleotide molecules of at least 400 nucleotides in length; and a second set of features each of which has single stranded second polynucleotide molecules of no more than 100 nucleotides in length. What is disclosed is that the magnitude of the range in each fraction is between 10 and 10,000 nucleotides (using the Examiner's calculations). That is, one fraction may have polynucleotides of a length X to (X + 10) while another may have a length of Y to (Y + 10,000). Nothing is stated in the foregoing about the absolute numbers of nucleotides in each fraction, but only the magnitude of the range of sizes of each fraction.

Accordingly, the Examiner has not pointed to anything in Chenchik et al. which actually anticipates the invention claimed in claims 1, 6-9 and the present rejection should therefore be withdrawn.

Paragraph 7

The Examiner next rejected claims 2 and 3 under 35 U.S.C. 102(b) as being anticipated by Chenchik et al. as defined by Stewart, or under 35 U.S.C. 103 as being obvious over the foregoing.

These rejections of claims 2 and 3 both extend on the Examiner's interpretation of Chenchik et al. discussed above. As discussed above, the Examiner has in fact not pointed to anything in Chenchik et al. which discloses features with polynucleotides of the claimed sizes in Chenchik's collected fractions (as distinct from the magnitude of the range in each fraction). Accordingly, these rejections should be withdrawn for this reason alone.

In addition to the above, the Examiner states that it would have been obvious to use the recited ratios of claims 2 or 3 (at least 10/1 or 20/1 of first to second polynucleotides) on the basis that "an experiment designed to analyze expressed sequences of at least 400 nucleotides, an array comprising mostly sequences of at

least 400 nucleotides would provide optimal analysis of the 400 nucleotide + sequences". It is assumed that the Examiner is proposing a modification to Chenchik et al.'s device although this is not expressly stated. If the Examiner is relying on something else, she is requested to identify what that is. Turning to Chenchik et al., that patent describes preparation of an array of "targets" according to size. The targets may be obtained from cells, tissues, organs, etc. and prepared by means which includes protease or nuclease digestion (Column 6, line 46 to Column 7). These "targets" are size separated and adhered to a surface (Column 8, lines 40-44). Nothing in Chenchik et al. describes or suggests how or why one could control this process to obtain the recited 10/1 or 20/1 ratios of the polynucleotides having at least 400 and less than 100 nucleotides. While one could presumably "throw away" fractions from a digest, for example, to ensure the claimed ratios are obtained this would result in losing sequences from which data would be obtained without any benefit suggested by Chenchik et al. For this reason alone (lack of motivation in Chenchik et al. to somehow make the changes suggested by the Examiner), the present rejection should be withdrawn.

Additionally, the Examiner assumes that for an experiment designed for analyzing sequences of at least 400 nucleotides one would use an array having mostly 400 nucleotides + for an optimal analysis. This is not at all clear since, depending on the assay one may want to use shorter probes to obtain higher specificity (see the discussion in the Summary on page 3, lines 21-27 of the present application). In any event, if the Examiner's argument was correct then one would want to use all features with more than 400 +nucleotides plus for most optimal analysis. However, the rejected claims 2 and 3 require that there be some such shorter length features present. For this additional reason (no motivation to use both types of features) the present rejection should be withdrawn.

Paragraph 9

The Examiner next rejected claims 2, 3, 10 and 15-21 under 35 U.S.C. 103(a) as being unpatentable over Adams et al. (US 6,060,288). All of the rejected claims now require that the first (at least 400 nt) and second (no more than 100 nt)

polynucleotides to be both single stranded. As discussed above under "Paragraph 5", Adams et al. does not disclose nor suggest such a feature. Accordingly, the present rejection should now be withdrawn. While there are additional features in some of the rejected claims that further distinguish them from the cited references, further discussion is not deemed necessary in view of the foregoing.

New Claim 41

This claim is similar to claim 1 before amendments, and does not require the first and second polynucleotides be single stranded. However, claim 41 does further require that each of the features of the second set contain a polynucleotide of only one sequence. In Adams et al. all the features may be less than 100 nucleotides in length before exposure to sample. This does not satisfy claim 41 (which requires features of at least 400 nt and features of no more than 100 nt). Once Adams et al. array is exposed to sample all features will begin hybridizing. Then there will not be features present with polynucleotide of no more than 100 nt and which each contains a polynucleotide of only one sequence (since there will be both hybridized and unhybridized molecules present on every feature). With regard to Chenchik et al., the Examiner has not pointed to anything in that reference where features with a same sequence are present (Chenchik et al. separating components only by size which therefore allows for different sequences of the same size or weight).

Accordingly, it is believed that claims 1-20 and 38-41 are now in condition for allowance. If the Examiner is of the view that there are any outstanding issues which might be resolved by means of a telephone conference, she is invited to call Gordon Stewart at (650)485-2386.

Respectfully submitted,

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APPENDIX

SHOWING ALL CLAIM AMENDMENTS NOW BEING MADE

1. (AMENDED) A polynucleotide array comprising:

(a) a first set of multiple features each of which has single stranded first polynucleotide molecules of at least 400 nucleotides in length; and

(b) a second set of features each of which has single stranded second polynucleotide molecules of no more than 100 nucleotides in length.

2. (AMENDED) A polynucleotide array according to claim 1 wherein ~~the~~ a ratio of the first set of features to the second set of features is at least 10/1.

3. (AMENDED) A polynucleotide array according to claim 1 wherein ~~the~~ a ratio of the first set of features to the second set of features is at least 20/1.

~~4. A polynucleotide array according to claim 1 wherein the first polynucleotide molecules are double stranded, and the second polynucleotides are single stranded.~~

5. A polynucleotide array according to claim 1 wherein the first polynucleotide molecules are from enzymatic processing of one or more longer polynucleotides, and the second polynucleotide molecules are synthetic.

6. A polynucleotide array according to claim 1 wherein the first polynucleotide molecules have a length of at least 500 nucleotides.

7. A polynucleotide array according to claim 1 wherein the first polynucleotide molecules have a length of at least 1000 nucleotides and the second polynucleotides have a length of no more than 80 nucleotides.

8. (AMENDED) A polynucleotide array according to claim 6 wherein the lengths of the first and second polynucleotides exclude the lengths of ~~any~~ a polynucleotide stilt portions if present.

9. A polynucleotide array according to claim 1 wherein the array features are arranged in a rectangle with second set features at least at the corners of the rectangle.

10. (AMENDED) A polynucleotide array according to claim 1 wherein the array features are arranged in lines, with at least some lines ~~having~~ including features of both the first and second sets of features and in which lines at least two features of the second set of features ~~which~~ are spaced apart by at least 70% of the first set features in the same line.

11. (AMENDED) A polynucleotide array according to claim 1 wherein at least 70% of a sequence of a second polynucleotide ~~sequence~~ molecule is not contained within a sequence of a first polynucleotide ~~sequence~~molecule.

12. (AMENDED) A polynucleotide array according to claim 11 wherein at least 70% of the sequences of more than half ~~majority of~~ the second polynucleotide molecules~~sequences~~ is not contained within a sequence of a first polynucleotide molecule~~sequence~~.

13. (AMENDED) A polynucleotide array according to claim 1 wherein none of the sequences of the second polynucleotide molecules~~sequences~~ is contained within a sequence of a first polynucleotide molecule.

14. A polynucleotide array according to claim 1 wherein the sequence of a second polynucleotide is contained within a first polynucleotide sequence.

15. (AMENDED) A kit comprising:
(a) a polynucleotide array having:

a first set of multiple features each of which has single stranded first polynucleotide molecules of at least 400 nucleotides in length;

a second set of features each of which has single stranded second polynucleotide molecules of no more than 100 nucleotides in length; and

(b) polynucleotide controls each of which is~~are~~, or their complements is~~are~~, at least 70% complementary to a sequences of a~~respective~~ second polynucleotides which is different for different ones of the controls.

16 (AMENDED) A kit according to claim 15 wherein each of the controls or their compliments is~~are~~ at least 90% complementary to a sequence~~s~~ of a second polynucleotide which is different for different ones of the controls. ~~respective second polynucleotides.~~

17. (AMENDED) A kit according to claim 15 wherein the controls ~~targets~~ are labeled.

18. (AMENDED) A kit according to claim 15 wherein a~~the~~ ratio of the first set of features to the second set of features is at least 10/1.

19. (AMENDED) A kit according to claim 15 wherein a~~the~~ ratio of the first set features to the second set of features is at least 20/1.

20. A kit according to claim 15 additionally comprising instructions to expose the array to a sample and the controls or their complements.

~~21. A kit according to claim 20 wherein first polynucleotide molecules are double stranded and the second polynucleotide molecules are single stranded.~~

22. A method of fabricating a polynucleotide array comprising:

(a) forming a first set of multiple features on a substrate each of which has first polynucleotide molecules of at least 400 nucleotides in length; and

(b) forming a second set of features on the substrate each of which has second polynucleotide molecules of no more than 100 nucleotides in length.

23. A method according to claim 22 wherein the forming of the first and second sets of features comprises depositing drops containing the first and second polynucleotides onto the substrate.

24. A method according to claim 22 wherein the ratio of first set features to second set features is at least 10/1.

25. A method of fabricating a polynucleotide array comprising:
(a) forming a first set of multiple features on a substrate each of which has first polynucleotide molecules of at least 400 nucleotides in length;
(b) forming a second set of features on the substrate each of which has second polynucleotide molecules of no more than 100 nucleotides in length;
the method additionally comprising:
(c) enzymatically processing polynucleotides to obtain the first polynucleotide molecules; and
(d) synthesizing the second polynucleotide molecules.

26. A method according to claim 25 additionally comprising evaluating a yield of the enzymatic processing of step (c) for a failed product sequence which has a yield below a predetermined threshold, and synthesizing at least one second polynucleotide of at least 25 nucleotides in length having a sequence the same as a sequence within the failed sequence.

27. A method according to claim 25 wherein a sequence of a second polynucleotide is contained within a first polynucleotide.

28. A method according to claim 22 wherein the first polynucleotides are double stranded and the second polynucleotides are single stranded.

29. A method of using a polynucleotide array of claim 1, comprising:

exposing the array to control targets such that the control targets hybridize at least 100 times more efficiently to respective second features than they to any of the first features.

30. A method according to claim 29 wherein the array is additionally simultaneously exposed to a sample.

31. A method according to claim 29 wherein the control targets are from a kit, or are complements of control polynucleotides from a kit, which kit also contains the array.

32. A method according to claim 30 wherein respective second set features hybridize more efficiently with control targets than any of the first set features hybridize to any control targets.

33. A method according to claim 29 wherein the targets are labeled.

34. A method according to claim 29 wherein the control polynucleotides are from a kit which also contains the array.

35. A method according to claim 29 additionally comprising:

reading the array to obtain an image representing the amount of polynucleotides which have bound to first and second set features;

evaluating locations of first features in the image using the locations of second features in the image.

36. A method of fabricating a polynucleotide array, comprising:

enzymatically processing one or more polynucleotides to obtain a set of polynucleotide molecules in respective fluid samples;

removing solid particles; and

ejecting drops of the fluid samples containing the polynucleotides onto a substrate through an orifice of a pulse jet, which orifice has an area of less than 1 mm^2.

37. A method according to claim 36 wherein the orifice has an area of less than .01 mm^2.

38. (NEW) A polynucleotide array according to claim 1 wherein features of the second set of features have the same polynucleotide.

39. (NEW) A polynucleotide array according to claim 1 wherein at least 70% of a sequence of each of the second polynucleotide molecules is not contained within a sequence of a first polynucleotide molecule.

40. (NEW) A polynucleotide array according to claim 1 wherein at least 70% of a sequence of each of the second polynucleotide molecules is not contained within a sequence of any of the first polynucleotide molecules.

41. (NEW) A polynucleotide array comprising:
(a) a first set of multiple features each of which has first polynucleotide molecules of at least 400 nucleotides in length; and
(b) a second set of features each of which has second polynucleotide molecules of no more than 100 nucleotides in length, each of which features contain a polynucleotide of only one sequence.